OPEN

PRS GLOBAL OPEN

ORIGINAL ARTICLE

Reconstructive

Significant Prognostic Factors Influencing the Survival Difference of Oral Tongue Squamous Cell Carcinoma

Sarinya Boonpoapichart, MD
Pattama Punyavong, MD
Kamonwan Jenwitheesuk, MD
Palakorn Surakunprapha, MD
Kengkart Winaikosol, MD

Background: Oral tongue squamous cell carcinoma is the most common malignancy in the oral cavity. Overall survival varies across many countries, and poor prognosis is prevalent in developing countries, including Thailand. Our study aimed to identify prognostic factors that affected survival for oral tongue cancer in Thailand.

Methods: We performed a retrospective study of 183 patients diagnosed with oral tongue squamous cell carcinoma between January 2012 and December 2016 and who underwent multidisciplinary treatment. The disease stage was classified by tumor-nodes-metastasis (TNM) staging system. The survival outcome was calculated and represented in median survival time. Univariate and multivariate Cox proportional hazards models were used to identify factors that impacted survival outcomes.

Results: A clear margin was achieved in 88.8% of the 125 operated patients. Radiotherapy was given to 115 patients (62.84%). The survival shown in Kaplan-Meier curves was significantly lower according to advanced TNM stage, poor histologic grade, nonsurgical treatment, and patients treated with radical neck dissection. Radiotherapy was a good prognostic factor [hazard ratio (HR) 0.25, $P = 0.022$]. Poor prognostic factors were body mass index less than 18.5 kg per m^2 (HR 3.03), vertical tumor dimension 20 mm or more (HR 5.84), non-well-differentiated grade tumor (HR 3.09), and operated cases with radical neck dissection (HR 4.29).

Conclusions: Surgical treatment can improve the survival outcome, whereas advanced stage and poor histological grading can worsen the overall survival. For oral tongue squamous cell carcinoma, radiotherapy was a good prognostic factor. On the contrary, a tumor with large vertical size, closed surgical margin, poor histologic grade, and radical neck dissection in the operated group were poor prognostic factors. *(Plast Reconstr Surg Glob Open 2021;9:e3889; doi: 10.1097/GOX.0000000000003889; Published online 26 October 2021.)*

INTRODUCTION

Tongue cancer comprises the majority of oral cavity cancer in Asian countries and worldwide.[1,2] It has the highest incidence rate (3.2:100,000) and mortality rate (0.6:100,000) among all other oral cavity cancers globally.[2]

In Thailand, the tongue is the most common anatomical site for oral cavity cancer, with an incidence rate of 2.2 and 1.0 per 100,000 in men and women, respectively, in 2011. Oral tongue squamous cell carcinoma (OTSCC) is the most frequent type of all tongue cancer.[3,4] Moreover, the number of patients in Thailand diagnosed with oral cancers increased continuously from 2004 to 2015.[5] As in the United States from 2007 to 2016, the incidence rate for both the base of tongue and anterior tongue cancer increased equally (1.8% per year on average).[6]

The 5-year survival rate in tongue cancer is the second-best of all oral cancers in many countries. The 5-year overall survival (OS) was 62.2% in China,[7] 62.8% in Germany,[8] and 68.1% in the United States.[9] However, in developing

From the Plastic & Reconstructive Unit, Department of Surgery, Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Received for publication July 8, 2021; accepted August 28, 2021.

DOI: 10.1097/GOX.0000000000003889

Disclosure: *The authors have no financial interest to declare in relation to the content of this article. This study was supported by Khon Kaen University Research Fund (grant no.: IN62317).*

Related Digital Media are available in the full-text version of the article on www.PRSGlobalOpen.com.

countries, the mortality rate was higher. In India, the 5-year relative survival rate in 2003 was 37.9%,[10] and the 3-year relative survival rate in Northeastern Thailand from 1985 to 2001 was as low as 29.3%.[11] Multiple risk factors have been identified as considerably associated with oral cancers. These factors are low socioeconomic status, betel-nut chewing, tobacco use, alcohol consumption, and viral infection (eg, Epstein Bar Virus, Human Simplex Virus-1, and Human papillomavirus type 16).[1,12–15]

More aggressive diseases, such as those with tumors invading adjacent structures, lymph node metastasis, or distant metastasis, resulted in poorer survival outcomes.[16] Many studies found a significant association of oral cancer with a low socioeconomic population.[1] These patients generally presented with regional and distant stages of disease due to late diagnosis and treatment. Multimodality of treatment, including radiation and chemotherapy, has been used to reduce the tumor size before surgery to achieve superior outcomes.[17–19] Nevertheless, there is a decrease in the quality of life regarding appearance, articulation, deglutition, taste, and sensation.[20] Numerous poor prognostic factors have been identified in oral squamous cell carcinoma (OSCC), such as tumor size greater than T2 according to TNM staging, nodal metastasis, involvement of pathological margin, histologic grade, perineural invasion (PNI), lymphovascular invasion, and extranodal extension (ENE).[21–24] The primary goal of this study was to discover the prognostic factors of OTSCC that significantly influenced survival differences in Thailand as, at present, only a few such studies have been reported.

PATIENTS AND METHODS

This study was approved by the Khon Kaen University Ethics Committee in Human Research, No. HE611620. A retrospective chart review from January 2012 to December 2016 that included all OTSCC patients with confirmed pathological diagnosis in Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, Thailand, was analyzed. All patients had a complete investigation and were classified based on the eighth edition of the American Joint Commission on Cancer TNM system before starting any modality of treatment. This study included a total of 183 cases.

General information, such as age, sex, occupation, education, underlying disease, weight, height, body mass index (BMI), and ASA classification, was recorded. Treatment details consisting of radiotherapy, chemotherapy, and surgical procedures were documented. In addition, tumor characteristics regarding TNM staging, histologic grade, the status of resected margin, ENE, and vertical dimension of tumor were collected.

The data were analyzed using STATA, version 10.1 (StataCorp LLC, College Station, Tex.). The quantitative data were presented as mean with SD, and a percentage was used to represent the categorical data. The survival time was calculated from the date of diagnosis to the date of death or the last day of this study (December 31, 2020), by the Kaplan-Meier method with a 95% confidence interval (95% CI). The significant difference in survival was calculated with the log-rank test. The univariate and multivariate Cox proportional hazards models were used to represent the crude and adjusted hazard ratio (HR), and a P value less than 0.05 was considered significant.

RESULTS

Patient demographic data are shown in Table 1. There were more female patients than male patients with OTSCC [113 (61.75%) female cases and 70 (38.25%) male cases]. Mean age and BMI were 55.77 ± 14.16 years and 20.89 ± 3.89 kg per m^2, respectively. Notably, the majority of patients had comorbidities (77, 42.08%). Most patients were farmers (130 cases, 71.04%), and most patients had education below a bachelor's degree (179 cases, 97.81%). Approximately one-third of all cases used tobacco (62 cases, 33.88%) and consumed alcohol (55 cases, 30.05%). The ASA classification in the population was shown greater in classes I and II (95.3%).

Tumor characteristics and treatment modality are presented in Table 2. The tumor staging was 13.66%, 29.51%, 24.04%, 28.96%, and 3.83% for T1, T2, T3, T4a, and T4b, respectively. One hundred and nineteen (65.03%) cases showed nodal metastasis as either N1 (24.59%), N2a (1.64%), N2b (21.86%), N2c (12.57%), or N3 (4.37%). In our study, distant metastasis was found in only eight cases (4.37%), and the majority of TNM staging was stage 4 (95 cases, 51.91%). Only 125 cases (68.31%) underwent tumor ablative surgery, of which 119 cases had either supraomohyoid neck dissection (SOHND) (60.50%), modified radical neck dissection (26.89%), or radial neck dissection (RND) (12.61%). Patients with tumor staging T2 or greater were treated with at least SOHND, whereas patients with clinical neck lymph node metastasis from stage N1 or higher received modified radical neck dissection or RND surgery. A clear margin was achieved in 111 cases (88.8%), whereas extranodal extension and perineural invasion were present in 15 cases (8.2%) and 12 cases

Table 1. Patient Demographic Data

Characteristics	n (%)
Total cases	183 (100%)
Gender	
Women	113 (61.75%)
Men	70 (38.25%)
Age at diagnosis (y, mean ± SD)	55.77 ± 14.16
Weight (kg, mean ± SD)	53.60 ± 11.13
BMI (kg/m^2, mean ± SD)	20.89 ± 3.89
Occupation	
Farmer	130 (71.04%)
Worker	18 (9.84%)
Businessman	14 (7.65%)
Officer	12 (6.55)
Monk	5 (2.73%)
Others	4 (2.19)
Education	
High school and below	179 (97.81%)
Bachelor and higher	4 (2.19%)
Smoking	62 (33.88%)
Betel-nut chewing	15 (8.2%)
Alcohol drinking	55 (30.05%)
Comorbidity	77 (42.08%)
ASA classification	
1	86 (47.00%)
2	89 (48.63%)
3	8 (4.37%)

Table 2. Perioperative Data

Characteristics	n (%)
Tumor staging	
T1	25 (13.66%)
T2	54 (29.51%)
T3	44 (24.04%)
T4a	53 (28.96%)
T4b	7 (3.83%)
Nodal staging	
N0	64 (34.97%)
N1	45 (24.59%)
N2a	3 (1.64%)
N2b	40 (21.86%)
N2c	23 (12.57%)
N3	8 (4.37%)
Metastasis	
M0	175 (95.63%)
M1	8 (4.37%)
TNM Staging	
1	21 (11.48%)
2	28 (15.30%)
3	39 (21.31%)
4	95 (51.91%)
Surgical treatment	
Yes	125 (68.31%)
No	58 (31.69%)
Margin status	
Clear	111 (88.8%)
Involved	14 (11.2%)
Neck dissection	119 (95.2%)
SOHND	72 (60.50%)
MRND	32 (26.89%)
RND	15 (12.61%)
Extranodal extension	
Yes	15 (8.2%)
No	168 (91.8%)
Perineural invasion	
Yes	12 (6.56%)
No	171 (93.44%)
Radiation treatment	
Yes	115 (62.84%)
No	68 (37.16%)
Chemotherapy	
Yes	53 (28.96%)
No	130 (71.04%)

(6.56%), respectively. The patients received adjuvant or definite radiation treatment in 115 cases (62.84%) and chemotherapy in 53 cases (28.96%).

The median OS of 1-, 3-, and 5-year patient survival after diagnosis with OTSCC are displayed in Table 3. Elaborated for the median survival time are such deleterious variables affecting the long-term outcome as late TNM staging, including stage 3 (42.73%, 95%CI 30.2–55.27) and stage 4 (27.09%, 95%CI 20.2–33.98); moderate, poor or undifferentiated tumor (11.33%, 95%CI 9.56–13.10); involved surgical margin (15.7%, 95%CI 12.58–18.82); radical neck dissection (12.47 %, 95%CI 11.30–13.64); and nonsurgery group (7.6%, 95%CI 5.41–9.79).

Supplemental Digital Content 1 shows the Kaplan-Meier curves of survival in OTSCC and describes the significant differences in survival relevant to TNM stage (P < 0.001), histologic grade (P < 0.001), surgical intervention (P < 0.001), and type of neck dissection (P = 0.001). (**See figure, Supplemental Digital Content 1,** which displays Kaplan-Meier curves 5-year overall survival of OTSCC by TNM staging, histopathological differentiation, surgery, type of neck dissection, and pathological margin. **http://links.lww.com/PRSGO/B816**.)

In the surgery group, there was no statistically significant difference of survival in either the positive or negative pathological margin group (P = 0.061).

Unadjusted HR calculated with the univariate Cox proportional hazards model is shown in Table 4. The analysis revealed that women (HR 1.58, 95%CI 1.07–2.32; P = 0.021), age 70.5 years or older (HR 2.06, 95%CI 1.33–3.19; P = 0.001), and BMI less than 18.5 kg per m^2 (HR 2.37, 95%CI 1.62–3.47; P < 0.001) significantly worsened the prognosis. The RND surgery group (HR 3.08, 95%CI (1.65–5.74; P < 0.001), the vertical dimension of tumor 20 mm or more (HR 4.61, 95%CI 2.45–8.67; P < 0.001), the presenting of ENE (HR 4.12, 95%CI 2.33–7.29; P < 0.001), and non-well-differentiated histologic grading group (HR 2.01, 95%CI 1.39–2.90; P < 0.001) decreased survival of OTSCC as well. On the other hand, surgical treatment had the benefit of improving survival outcome substantially (HR 0.21, 95%CI 0.15–0.31; P < 0.001).

Table 5 shows the results of applying the multivariate Cox proportional hazards model to identify the important prognostic factors. The adjusted HR disclosed that a BMI less than 18.5 kg per m^2 (adjusted HR 3.03, 95%CI 1.11–8.25), a vertical dimension of tumor 20 mm or more (adjusted HR 5.84,

Table 3. Median Survival Time: 1-, 3-, and 5-year Survival

	Median Survival Time (mo) (95% CI)	1-year Survival (95% CI)	3-year Survival (95% CI)	5-year Survival (95% CI)
TNM staging				
Stage 1	83.39 (70.37–96.41)	95.24 (70.72–99.32)	85.71 (61.97–95.16)	76.19 (51.94–89.33)
Stage 2	67.86 (53.54–82.18)	85.71 (66.29–94.38)	67.86 (47.32–81.8)	64.09 (43.52–78.82)
Stage 3	42.73 (30.2–55.27)	71.79 (54.88–83.28)	41.03 (25.69–55.76)	35.9 (21.38–50.64)
Stage 4	27.09 (20.2–33.98)	41.05 (31.13–50.7)	21.05 (13.53–29.71)	18.95 (11.81–27.38)
Histologic grade				
Well	29.70 (0.00–61.16)	70.34 (61.21–77.71)	48.31 (39.05–56.95)	44.74 (35.6–53.46)
Moderate/poor/undifferentiated	11.33 (9.56–13.10)	43.08 (30.93–54.64)	24.62 (14.97–35.53)	20 (11.34–30.43)
Surgery				
No	7.6 (5.41–9.79)	24.14 (14.09–35.66)	6.9 (2.22–15.29)	6.9 (2.22–15.29)
Yes	57.63 (50.27–64.99)	77.6 (69.24–83.95)	55.2 (46.07–63.41)	49.4 (40.34–57.82)
Type of neck surgery				
SOHND	63.16 (54.14–72.18)	80.56 (69.39–87.99)	65.28 (53.09–75.03)	58.16 (45.89–68.59)
MRND	26.37 (15.7–97.57)	75 (56.18–86.63)	46.88 (29.15–62.77)	46.88 (29.15–62.77)
RND	12.47 (11.30–13.64)	60 (31.76–79.65)	13.33(2.19–34.57)	13.33 (2.19–34.57)
Surgical margin				
Negative	60.06 (52.3– 67.82)	77.48 (68.52–84.18)	58.56 (48.82–67.07)	52.1 (42.4–60.92)
Involved	15.7 (12.58– 18.82)	78.57 (47.25–92.54)	28.57 (8.83–52.37)	28.57 (8.83–52.37)

Table 4. Unadjusted HR by the Univariate Cox Proportional Hazards Model Predicting Overall Survival

Factors	HR	95% CI	*P*
Gender			
Men	1		
Women	1.58	(1.07–2.32)	0.021
Age (y)			
<70.5	1		
≥70.5	2.06	(1.33–3.19)	0.001
BMI (kg/m²)			
≥18.5	1		
<18.5	2.37	(1.62–3.47)	<0.001
ASA classification			
1	1		
2–3	1.76	(0.95–3.29)	0.075
Vertical dimension of tumor			
<20 mm	1		
≥20 mm	4.61	(2.45–8.67)	<0.001
Surgery			
No	1		
Yes	0.21	(0.15–0.31)	<0.001
Extranodal extension			
No	1		
Yes	4.12	(2.33–7.29)	<0.001
Perineural invasion			
No	1		
Yes	1.32	(0.67–2.60)	0.428
Resected margin			
Negative	1		
Positive	1.89	(0.96–3.73)	0.065
Length of free margin			
>3 mm	1		
≤3 mm	2.37	(1.27–4.44)	0.007
Differentiation			
Well	1		
Moderate + poor	2.01	(1.39–2.90)	<0.001
Type of neck surgery			
SOHND + MRND	1		
RND	3.08	(1.65–5.74)	<0.001
Radiation			
No	1		
Yes	0.83	(0.57–1.21)	0.341

Table 5. Adjusted HR by Multivariate Cox Proportional Hazards Model Predicting Overall Survival

Factors	Crude HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
BMI		<0.001		0.030
≥18.5	1		1	
<18.5	2.37 (1.62–3.47)		3.03 (1.11–8.25)	
Vertical dimension of tumor		<0.001		0.004
<20 mm	1		1	
≥20 mm	4.61 (2.45–8.67)		5.84 (1.75–19.54)	
Differentiation		<0.001		0.024
Well	1		1	
Moderate + poor	2.01 (1.39–2.90)		3.09 (1.16–8.24)	
Type of neck surgery		<0.001		0.017
SOHND + MRND	1		1	
RND	3.08 (1.65–5.74)		4.29 (1.3–14.17)	
Postoperative radiotherapy		0.341		0.022
No	1		1	
Yes	0.83 (0.57–1.21)		0.25 (0.07–0.82)	

95%CI 1.75–19.54), a histologic grade with moderate or poor differentiated tumor (adjusted HR 3.09, 95%CI 1.16–8.24), and the group of operated cases with RND (adjusted HR 4.29, 95%CI 1.3–14.17) had detrimental effects on survival, with a *P* value less than 0.05. Lastly, radiotherapy was the only factor that had the advantage of increasing overall survival (adjusted HR 0.25, 95%CI 0.07–0.82; $P = 0.022$).

DISCUSSION

Tongue cancer is the most frequent diagnosis of all oral cancers, and OTSCC is the primary pathological type.[4] Several studies in Thailand reported prognostic factors that affect survival outcome. In the United States during 2006–2015, according to the SEER database of head and neck cancer, most patients were men older than 50 years.[25] For oral cancer, the average ages of non-Asian and Asian patients in a multicenter study between 2005 and 2014 were 69.99 years and 56.37 years, respectively.[4] Similarly, the mean age of the 183 patients in our study was 55 years. In other studies,[4,26] the number of male patients was generally higher than the number of female patients diagnosed with OTSCC. In our current study, however, we found a higher ratio of female-to-male patients (1.6:1). Since 1985, a high percentage of women with oral cancer have been found predominantly in northeastern Thailand.[11,15] The higher ratio of female patients can be explained by a previous study by Kampangsri et al, which showed that, in the past, betel-nut chewing was a habit common among Thai people, especially among women, who chewed betel nuts daily starting at an early age.[15] Betal nuts have been reported to contain carcinogens, such as polycyclic aromatic hydrocarbons, polonium 210, and nitrosamine, all of which subsequently cause precancerous lesions, including oral leukoplakia and oral submucous fibrosis.[27]

Most patients who presented to the hospital in the late stage expressed difficulty chewing and swallowing, which consequently caused weight loss associated with low BMI and malnutrition. The average BMI in our study was 20.89 kg per m², which can adversely influence disease prognosis. Correspondingly, low pretreatment BMI (<25.0 kg/m²) was found to have a detrimental effect on OSCC survival in a cross-sectional study that included 320 patients.[28]

In this current study, most of the population (71.04%) worked in agriculture, a manifestation of low socioeconomic status in Thailand. A previous study also found low socioeconomic status to be a risk factor for oral cancer.[1] It has long been accepted that smoking and alcohol consumption are oral cancer risk factors.[12–14] However, we discovered that only 33.88% of the patients smoked, and 30.05% consumed alcohol in our study. Additionally, 15 cases (8.2%) in our study had a history of betel-nut chewing. This result differed from the Kampangsri et al study, which reviewed 17,388 patients and concluded that betel-nut chewing was presented by 15.9% of the total subjects and the important factor in the upper aerodigestive tract cancer. Our study, however, contained an inadequate population and failed to recognize betel-nut chewing as a significant risk factor. Similarly, alcohol drinking and tobacco smoking were less favorable in women and thus considered insignificant.[15]

Out of the 183 cases in our study, 125 patients (68.31%) underwent surgery. According to the data categorized by tumor staging and TNM staging in Table 2, most cases presented with T3 and T4 (56.83%); hence the diagnoses were primarily in TNM stages 3 and 4 (73.22%). In a study published by Rogers et al, 144 OTSCC patients of 489 OSCC patients who underwent surgery had a 5-year

OS equal to 64%. The tumors were primarily in the T1–T2 status.[29] In contrast, the 5-year OS in our study was only 49.4% in the surgery group due to the patients presenting late with high-risk tumor stages T3–T4. Although patients presented with cancer in most cases, a clear surgical margin as high as 88% was obtained in our study. In the nonoperated group, most cases had at least a locally invasive tumor and advanced disease stage. Instead of surgery, this patient group chose as their primary treatment complementary and alternative medicine or other nonoperative modalities, typical to the deep-seated paranormal beliefs of the low socioeconomic population in northeastern Thailand. The bad prognosis of these patients aggravated the decline of their overall survival outcome.

The pathological result in this study reported that ENE and PNI were present in small percentages (8.2% and 6.56%, respectively). However, the univariate Cox proportional hazard analysis revealed that ENE markedly altered the OTSCC prognosis outcome (HR 4.12, $P < 0.001$). Thus, multiple ENE studies confirmed its importance as a prognostic factor for OSCC. Comparing ENE-negative and ENE-positive groups in the lymph node metastasis group, the ENE-positive group had a lower survival outcome.[30] On the contrary, our study found PNI an insignificant prognostic factor. Unlike in our result, a case-control study of PNI in OSCC by Laske et al demonstrated that PNI had a critical impact on survival outcome.[31] As mentioned earlier, the insignificant result probably came from the small number of PNI presented in our patients.

The Kaplan-Meier graph displayed in Supplemental Digital Content 1 indicates that early TNM stages and well-differentiated tumors can predict a good survival outcome in OTSCC. The survival was significantly higher in patients who underwent surgery (median survival 57.63 months versus 7.6 months; $P < 0.001$). In the operated group, there were 119 patients with neck dissection surgery. Comparing the groups revealed that patients who underwent SOHND had the greatest survival. The modified radical neck dissection and RND groups had inferior survival outcomes successively ($P = 0.001$). These outcomes corresponded precisely with the nature of the disease in malignancy. In patients with bulky cervical lymph node metastasis or extensive soft tissue involved in an extracapsular spread, RND was performed. Therefore, patients who underwent multiple nodal metastases usually had a detrimental prognosis. According to the surgical margin, surgery that can gain a clear margin had a superior survival outcome over the involved margin group (5-year OS 52.1% versus 28.57%; $P = 0.061$). The lack of statistically significant difference in survival was most likely due to the small number of positive margin group cases in our study. Dissimilarly, Rogers et al reported, via a large retrospective study of 489 oral cancer patients, a remarkable difference in survival between clear and involved margins (5-year OS 66% versus 35%).[29]

A small study conducted by Geum et al in Korea consisted of 37 patients with 11 cases of tongue cancer. It revealed that TNM stage, cervical lymph node metastasis, and recurrence after surgery had critically impacted the 5-year survival of oral cancer.[16] Montoro published a similar prognostic factors report consisting of 45 oral squamous cell carcinoma cases in Brazil, which indicated that neck node metastasis had a notable effect on survival.[22] The pathological study revealed that an early tongue cancer stage (T1 and T2 with N0M0 stage) with a depth of invasion greater than 4 mm, a high worst pattern of invasion, and high tumor budding were the critical indicators for predicting prognosis in OTSCC.[32] In an additional study of histologic grade, a poor or undifferentiated tumor was also strongly associated with lowering the survival of oral squamous carcinoma.[23]An extensive database that included a total of 2082 OSCC patients with the tongue as the prominent anatomical location revealed several independent prognostic factors (ie, age < 60 years, presence of severe comorbidities, positive margin status, presence of vascular invasion, presence of PNI, T3-4 stage, and pN2-3 stage).[26]

In our study, the univariate Cox proportional hazards model disclosed that surgery was the only good prognostic factor (HR 0.21; 95% CI 0.15–0.31; $P < 0.001$). This calculation may have been reflected in finding that survival improved for patients who presented with a late disease stage but had surgery. Many meaningful poor prognostic factors include women (HR 1.58; 95% CI 1.07–2.32; $P = 0.021$), age 70.5 years or older (HR 2.06; 95% CI 1.33–3.19; $P = 0.001$), BMI less than 18.5 kg per m^2 (HR 2.37; 95% CI 1.62–3.47; $P < 0.001$), vertical dimension of tumor 20 mm or more (HR 4.61; 95% CI 2.45–8.67; $P < 0.001$), presence of ENE (HR 4.12; 95% CI 2.33–7.29; $P < 0.001$), surgical margin 3 mm or less (HR 2.37; 95% CI 1.27–4.44; $P = 0.007$), histologic grade with moderate, poor, or undifferentiated tumor (HR 2.01; 95% CI 1.39–2.90; $P < 0.001$), and RND in operated patients (HR 3.08, 95%CI 1.65–5.74; $P < 0.001$). Older age tends to lower the survival of any disease, and low BMI is relevant to oral cavity cancer in general. Our study recognizes that these factors are confounding. The high ratio of women in our study population resulted in a bias in our analysis. Therefore, our study did not conclude female gender a true poor prognostic factor. Vertical tumor size had been shown beneficial for computer tomography-based preoperative measurements for predicting survival. Nevertheless, identifying its implication on clinical significance requires further investigation. The extent of nodal extension, a surgical margin 3 mm or less, and a moderate or poor histologic grade are deleterious factors for oral cavity cancers. Meanwhile, the univariate Cox proportional hazards model analysis revealed that ASA classification, PNI, involved surgical margin group, and radiotherapy were insignificant. Finally, after adjusting the evaluation from the multivariate Cox proportional hazards model, adjuvant radiotherapy was a remarkably good prognostic factor in OTSCC (adjusted HR 0.25; 95%CI 0.07–0.82, $P = 0.022$). As a standard practice, operated patients with extranodal extensions, positive surgical margin or presenting other adverse risk factors (eg, multiple positive lymph nodes, perineural invasion, lymphovascular invasion, pathological T3 or T4 primary, and positive level IV or V lymph nodes), and who received radiotherapy were shown to have a better survival outcome.

Strength and Limitation of the Study

Our study, consisting mainly of the advanced stage of OTSCC across a large population, disclosed an advantage of surgery on survival even in advanced stages compared with the nonoperated group, neither clear nor involved surgical margin achievement. In addition, our results showed a predominantly higher ratio of female patients compared with other studies, which may have consequently presented a population biased toward fewer tobacco smoking and alcohol consumption incidences. However, some parameters, such as the positive margin group and PNI, were presented in a few cases, and thus, this might consequently affect the insignificant difference of survival outcomes.

CONCLUSIONS

In this study, we comprehensively analyzed factors for predicting the survival of OTSCC. We found that surgery and radiotherapy were good prognostic factors, whereas presenting a vertical dimension of tumor 20mm or more, the presence of ENE, a surgical margin 3mm or less, a histologic grade with a moderate or poor differentiated tumor, and an RND in an operated group were poor prognostic factors.

Kengkart Winaikosol, MD
Department of Surgery, Faculty of Medicine
Khon Kaen University, 123 Mittraparp Highway
Muang District, Khon Kaen 40002
Thailand
E-mail: kengkawi@kku.ac.th

ACKNOWLEDGMENT

The authors thank Mr. Kevin McCracken for assistance with the English language presentation of the article under the aegis of the Khon Kaen University Publication Clinic, Thailand.

REFERENCES

1. Krishna Rao S, Mejia G, Roberts-Thomson K et al. Epidemiology of oral cancer in Asia in the past decade—an update (2000–2012). *Asian Pac J Cancer Prev.* 2013;14:5567–5577.
2. Rettig EM, D'Souza G. Epidemiology of head and neck cancer. *Surg Oncol Clin N Am.* 2015;24:379–396.
3. Tangjaturonrasme N, Vatanasapt P, Bychkov A. Epidemiology of head and neck cancer in Thailand. *Asia Pac J Clin Oncol.* 2018;14:16–22.
4. Dhanuthai K, Rojanawatsirivej S, Thosaporn W, et al. Oral cancer: a multicenter study. *Med Oral Patol Oral Cir Bucal.* 2018;23:e23–e29.
5. Arunpraphan S. The trends of oral cavity and pharyngeal cancer incidence in Thailand, 2004–2015. *Thai Dental Public Health Journal.* 2019;24:55–67.
6. Ellington TD, Henley SJ, Senkomago V, et al. Trends in incidence of cancers of the oral cavity and pharynx - United States 2007-2016. *MMWR Morb Mortal Wkly Rep.* 2020;69:433-438.
7. Chen SW, Zhang Q, Guo ZM, et al. Trends in clinical features and survival of oral cavity cancer: fifty years of experience with 3,362 consecutive cases from a single institution. *Cancer Manag Res.* 2018;10:4523–4535.
8. Jehn P, Dittmann J, Zimmerer R, et al. Survival rates according to tumour location in patients with surgically treated oral and oropharyngeal squamous cell carcinoma. *Anticancer Res.* 2019;39:2527–2533.
9. SEER. Cancer of the tongue – cancer stat facts. Available at https://seer.cancer.gov/statfacts/html/tongue.html. Accessed April 26, 2021.
10. Swaminathan R, Selvakumaran R, Esmy PO, et al. Cancer pattern and survival in a rural district in South India. *Cancer Epidemiol.* 2009;33:325–331.
11. Vatanasapt P, Suwanrungruang K, Kamsa-Ard S, et al. Epidemiology of oral and pharyngeal cancers in Khon Kaen, Thailand: a high incidence in females. *Asian Pac J Cancer Prev.* 2011;12:2505-2508.
12. Johnson N. Tobacco use and oral cancer: a global perspective. *J Dent Educ.* 2001;65:328–339.
13. Sarich P, Canfell K, Egger S, et al. Alcohol consumption, drinking patterns and cancer incidence in an Australian cohort of 226,162 participants aged 45 years and over. *Br J Cancer.* 2021;124:513–523.
14. Muwonge R, Ramadas K, Sankila R, et al. Role of tobacco smoking, chewing and alcohol drinking in the risk of oral cancer in Trivandrum, India: a nested case-control design using incident cancer cases. *Oral Oncol.* 2008;44:446–454.
15. Kampangsri W, Vatanasapt P, Kamsa-Ard S, et al. Betel quid chewing and upper aerodigestive tract cancers: a prospective cohort study in Khon Kaen, Thailand. *Asian Pac J Cancer Prev.* 2013;14:4335–4338.
16. Geum DH, Roh YC, Yoon SY, et al. The impact factors on 5-year survival rate in patients operated with oral cancer. *J Korean Assoc Oral Maxillofac Surg.* 2013;39:207–216.
17. Magrini SM, Buglione M, Corvò R, et al. Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II trial. *J Clin Oncol.* 2016;34:427–435.
18. Husain ZA, Burtness BA, Decker RH. Cisplatin versus cetuximab with radiotherapy in locally advanced squamous cell carcinoma of the head and neck. *J Clin Oncol.* 2016;34:396–398.
19. Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. *J Clin Oncol.* 2014;32:2735–2743.
20. Dzebo S, Mahmutovic J, Erkocevic H. Quality of life of patients with oral cavity cancer. *Mater Sociomed.* 2017;29:30–34.
21. Suresh GM, Koppad R, Prakash BV, et al. Prognostic indicators of oral squamous cell carcinoma. *Ann Maxillofac Surg.* 2019;9:364–370.
22. Montoro JRMC, Hicz HA, de Souza L, et al. Prognostic factors in squamous cell carcinoma of the oral cavity. *Braz J Otorhinolaryngol.* 2008;74:861–866.
23. Thomas B, Stedman M, Davies L. Grade as a prognostic factor in oral squamous cell carcinoma: a population-based analysis of the data. *Laryngoscope.* 2014;124:688–694.
24. Surakunprapha P, Thanasarnwimon T, Sangkhamanon S et al. The length of peri-neural spreading in clinically mandibular invaded oral cavity squamous cell carcinoma. *J Med Assoc Thai.* 2020;103:459–464.
25. Kim YJ, Kim JH. Increasing incidence and improving survival of oral tongue squamous cell carcinoma. *Sci Rep.* 2020;10:7877.
26. Zanoni DK, Montero PH, Migliacci JC, et al. Survival outcomes after treatment of cancer of the oral cavity (1985–2015). *Oral Oncol.* 2019;90:115–121.
27. Song H, Wan Y, Xu YY. Betel quid chewing without tobacco: a meta-analysis of carcinogenic and precarcinogenic effects. *Asia Pac J Public Health.* 2015;27:NP47–NP57.
28. Chang WC, Yang CY, Lin CS, et al. Pretreatment body mass index as a prognostic predictor in patients with oral squamous cell carcinoma. *Clin Oral Investig.* 2020;24:2781–2788.
29. Rogers SN, Brown JS, Woolgar JA, et al. Survival following primary surgery for oral cancer. *Oral Oncol.* 2009;45:201–211.
30. Shaw RJ, Lowe D, Woolgar JA, et al. Extracapsular spread in oral squamous cell carcinoma. *Head Neck.* 2010;32:714–722.
31. Laske RD, Scholz I, Ikenberg K, et al. Perineural invasion in squamous cell carcinoma of the oral cavity: histology, tumor stage, and outcome. *Laryngoscope Investig Otolaryngol.* 2016;1:13–18.
32. Almangush A, Bello IO, Keski-Säntti H, et al. Depth of invasion, tumor budding, and worst pattern of invasion: prognostic indicators in early-stage oral tongue cancer. *Head Neck.* 2014;36:811–818.